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ORIGINAL ARTICLE

Fetal growth and maternal glomerular filtration rate: a systematic review

Hanna M. Vesterinen[1], Paula I. Johnson[1,2], Dylan S. Atchley[1], Patrice Sutton[1], Juleen Lam[3], Marya G. Zlatnik[4], Saunak Sen[5], and Tracey J. Woodruff[1]

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Abstract

Objective: Glomerular filtration rate (GFR) may influence concentrations of biomarkers of exposure and their etiologic significance in observational studies of associations between environmental contaminants and fetal growth. It is unknown whether the size of a developing fetus affects maternal GFR such that a small fetus leads to reduced plasma volume expansion (PVE), reduced GFR and subsequent higher concentrations of biomarkers in maternal serum. Our objective was to answer the question: "Is there an association between fetal growth and maternal GFR in humans?"

Methods: We adapted and applied the Navigation Guide systematic review methodology to assess the evidence of an association between fetal growth and GFR, either directly or indirectly via reduction in PVE.

Results: We identified 35 relevant studies. We rated 31 human and two non-human observational studies as "low" quality and two experimental non-human studies as "very low" quality. We rated all three evidence streams as "inadequate". The association between fetal growth and GFR was "not classifiable" according to pre-specified definitions.

Conclusions: There is currently insufficient evidence to support the plausibility of a reverse causality hypothesis for associations between exposure to environmental chemicals during pregnancy and fetal growth. Further research would be needed to confirm or disprove this hypothesis.

Keywords

Fetal growth, glomerular filtration rate, perfluorooctanoic acid, plasma volume expansion, reproductive environmental health, reverse causality, the navigation guide

History

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Background

Impaired prenatal growth is an indicator for adverse developmental health impacts that can manifest across the human lifespan [1,2]. We conducted a systematic review that found greater levels of perfluorooctanoic acid (PFOA) that are associated with impaired fetal growth in humans [3]. However, there is some literature that suggests the possibility of ''reverse causality'' [4]; that is, smaller fetuses lead to greater concentrations of environmental chemicals measured in maternal serum via a reduction in plasma volume expansion (PVE) and reduced glomerular filtration rate (GFR; Figure 1). Pregnancy is associated with PVE to accommodate the growing fetus and an increase in kidney function, including GFR [5,6] (Supplementary Material 1); therefore, the reverse causality hypothesis posits that a smaller fetus leads to a reduction in GFR directly or indirectly through a lower PVE. In our review of PFOA we had robust experimental animal evidence that mirrored the human evidence and for which the reverse causality hypothesis would not apply [7]; however, experimental evidence may not always be available to augment the interpretation of observational human studies in environmental health. Thus, we assessed the strength of the evidence for the reverse causality hypothesis using the Navigation Guide systematic review method [8].

Methods

We adapted and applied the Navigation Guide systematic review methodology for environmental health [9] to assess the strength of evidence for a direct or indirect relationship between fetal growth and GFR. We conducted our systematic review as outlined beforehand in a protocol which is available online (http://prhe.ucsf.edu/prhe/) and summarized below.

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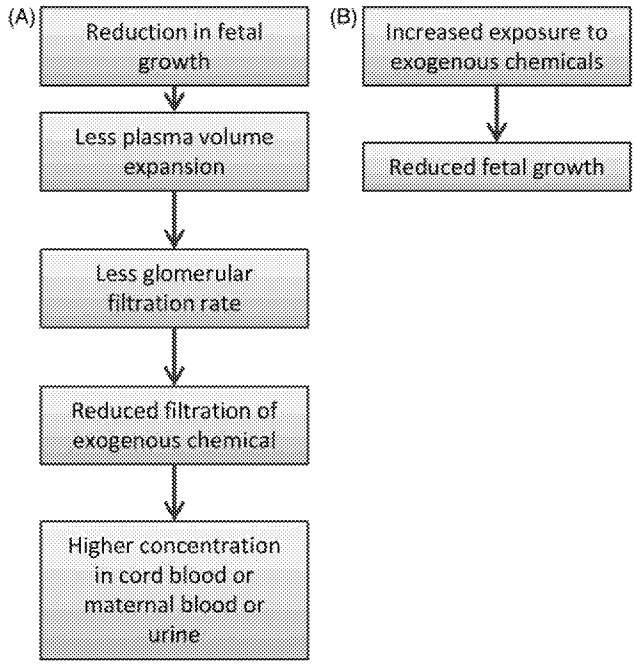

Figure 1. A flow diagram outlining two potential hypotheses for the relationship between exogenous chemicals and fetal growth. Changes in fetal growth may affect the concentration of measurable chemicals due to changes in the maternal plasma volume and subsequent changes in maternal GFR (A); or increased exposure to exogenous chemicals may cause changes in fetal growth (B). The Navigation Guide has previously evaluated the evidence in support of hypothesis B [7,8], whereas the present review evaluates the evidence in support of hypothesis A.

Step 1: Specify the study question

We used a ''PECO'' (Participants, Exposure, Comparator, Outcome) aid to outline the study question [modified from [10] (Supplementary Material 2)]. Our objective was to answer the question ''Is there an association between fetal growth and maternal GFR in humans?'' We considered the following potential direct and indirect relationships between fetal growth and GFR: (1) the direct relationship between fetal growth and GFR (Supplementary Figure 1A, arrow i); OR (2) between fetal growth and PVE (Supplementary Figure 1A, arrow ii); AND (3) between PVE and GFR (Supplementary Figure 1A, arrow iii). We evaluated both human and non-human mammalian models of the relationships described in Supplementary Figure 1.

Herein, we use the terms PVE or GFR as referring to any suitable measures of maternal PVE or GFR, respectively.

Step 2: Select the evidence

We conducted our online search, study selection criteria and data collection as described in the online protocol. Briefly, we searched four online databases (Biosis Previews, ISI Web of Science, Pubmed and Embase) on 15 August 2013 and selected relevant studies using pre-specified inclusion and exclusion criteria.

Step 3: Rate the quality and strength of the evidence

To rate the quality and strength of the evidence we: (1) assessed each included study for risk of bias; (2) rated the overall quality across all studies separately for the human and non-human evidence; and (3) rated the overall strength of the evidence across the combined body of all human and non-human studies. These steps are described in detail in the online protocol. Briefly, we rated the risk of bias across seven domains, five of which were the same across evidence streams. Next, we evaluated the data from each study. We conducted a quantitative analysis on studies which reported the study subjects, a mean score and variance (standard error (SE) or standard deviation (SD)) and either: dichotomized birth weight into average for gestational age and small for gestational age; or compared two groups with different mean birth weights.[1] Additionally, we conducted *post-hoc* analyses on raw data, when available, for the independent and dependent variable (individual participant data; IPD). For studies that dichotomized birth weight, we calculated the difference in mean effect sizes (see online protocol). For studies which reported individual participant data, we performed a *post-hoc* regression analysis using independent and dependent variables as described in Supplementary Figure 1 and using the beta-coefficient and 95% confidence intervals (CI) as our effect size estimate. Studies which did not report data suitable for a *post-hoc* analysis were assessed qualitatively.

Next, we rated the quality of the evidence across studies. Possible ratings for quality of a body of evidence were ''high'', ''moderate'' or ''low''. Ratings were determined beforehand by assigning an initial quality rating to each body of evidence, then considering factors that would lead us to downgrade and/or upgrade the rating, based on characteristics of the studies included in that body of evidence. We assigned initial ratings beforehand of ''moderate'' to observational human studies and ''high'' to experimental mammalian studies as described in detail previously [3,7]. Additionally, we considered the body of observational non-human studies identified in this review to be sufficiently similar in design to observational human studies and thus assigned beforehand an initial rating of ''moderate''. We rated the quality of human and non-human evidence separately according to five down-grade factors and three upgrade factors (see protocol).

Finally, we assigned one of the following possible ratings for the strength of evidence across studies: ''sufficient evidence of an association'', ''limited evidence of an association'', ''inadequate evidence of an association'' or ''evidence of lack of association''.

Integrating the strength of human and non-human evidence streams

We integrated the results of the strength of human and non-human evidence assessment as described previously [3,7] to achieve an overall statement on the evidence of an association between fetal growth and GFR: ''known to be associated'',

[1]For comparisons on which we were able to calculate a difference in means (Mdi) effect size, only four outcomes used sufficiently similar exposure groups (birth weight less than the 10th percentile for gestational age), comparator groups (birth weight above the 10th percentile for gestational age) and outcomes (absolute plasma volume); however, differences in the timing of assessment (gestational week) meant we were not able to combine these in a meta-analysis, and the small number of comparisons did not permit us to perform an analysis with time of assessment as a covariate, and thus no meta-analysis was conducted.

''probably associated'', ''possibly associated'', ''probably not associated'' or ''not classifiable''(Figure 3).

Results

Included studies

We identified 5261 publications in our literature search (Supplementary Figure 2 and Supplementary Material 3) of which 29 were considered relevant and an additional six were identified through hand searching. Thus, 35 studies (33 full publications and 2 human observational-study meeting abstracts) published between 1954 and 2012 (median 1992) were included in the systematic review as follows: 31 observational human studies, 2 observational mammalian studies (1 each in cows and dogs) and 2 experimental mammalian studies (1 each in rats and ewes) (full study details are available online at (http://prhe.ucsf.edu/prhe/).

Risk of bias of individual studies

We rated risk of bias across seven domains individually for the 33 full publications (Supplementary Figure 3). The majority of human studies were considered ''low'' or ''probably low'' risk of bias for blinding (83%), recruitment strategy (76%), confounding (66%), incomplete outcome data (62%), selective outcome reporting (97%) and other sources of bias (100%). For conflict of interest, we considered a large proportion of studies to be at ''probably high'' risk of bias (66%), because neither a funding source nor a conflict or interest statement was reported. Approximately, a third of studies were also considered ''probably high'' risk or ''high'' risk for confounding (34%) and ''probably high'' risk for incomplete outcome data (38%). For non-human observational studies, we rated both studies ''probably high'' risk for confounding: one study did not adjust for the age or weight of the animals [11] and the second study did not report the maternal or gestational age [12]. Additionally, we rated this second study as ''probably high'' risk for conflict of interest as no statement or funding source was reported. For allocation concealment, blinding and incomplete outcome data we rated both non-human experimental studies as ''probably high'' risk of bias and we rated one experimental mammalian study as ''probably high'' risk for randomization.

Summary of findings

We described the expected change in normal pregnancy for all of the outcome measures in Supplementary Material 1. The relationships assessed in each study and the graphical or qualitative results are presented in Figure 2, Supplementary Figures 4 to 7 and Supplementary Materials 4 to 7.

Quality of the body of evidence

We downgraded the overall quality of the human, observational mammalian and experimental mammalian studies according to the rationale reported in Supplementary Material 8.

- We downgraded the body of human studies ($N=31$) from the initial rating of ''moderate'' to ''low'' due to inconsistency of findings among the studies (see ''Methods'' section for details). Specifically, while we found consistent evidence of an association among studies reporting the relationship between birth weight and PVE, studies of the relationship between GFR and birth weight were inconsistent and the majority of these studies were small (median sample size of 9, range 9 to 283). Additionally, although we considered there should be a dose-response relationship between hemoglobin levels and odds of SGA, there was no evidence of a dose-response relationship between fetal growth and GFR.
- We downgraded the body of observational mammalian studies ($N=2$) from ''moderate'' to ''low'' because of imprecision as judged by wide confidence intervals. Specifically, we considered the two studies to be too small (total sample size of $n=65$) to provide precise effect estimates.
- We downgraded the body of experimental mammalian studies ($N=2$) from our initial rating of ''high'' to ''low'' based on a high risk of bias across studies, indirectness and imprecision. Both studies were ''probably high risk of bias'' for the allocation concealment, blinding and incomplete outcome data domains, and one study was also ''probably high risk of bias'' for randomization (Supplementary Figure 3). One study used an indirect measure of fetal growth (the product of estimated chest girth and estimated fetal weight to chest girth ratio using growth catheters), and we considered both studies to be too small ($n=23$ in total) to provide precise effect estimates (Supplementary Figure 7).

Strength of the body of evidence

We assessed the strength of the evidence by considering the quality ratings described above with our assessment of the direction of effect and our confidence in the effect. We found the strength of the evidence of an association between fetal growth and GFR to be ''inadequate'' (see online Protocol for definitions) for both the human and non-human evidence streams (Supplementary Material 9).

- Our rationale for ''inadequate'' human studies was based on the ''low'' quality of evidence, the indeterminate direction of effect and a lack of confidence in the effect between fetal growth and GFR, either directly or via change in PVE. Although we were confident in the effect between fetal growth and PVE, based on data from the two largest studies [13,14], we had low confidence in the evidence on the association between fetal growth and GFR, or PVE and GFR. Thus, a new, well-designed and adequately powered study would be likely to change our certainty in the strength of the effect between fetal growth and GFR, or between PVE and GFR.
- Our rationale for ''inadequate'' evidence of an association from observational mammalian studies was based on the ''low'' quality of the evidence, the indeterminate direction of effect and a lack of confidence in the effect estimate because the data were limited to one small study each on the relationship between fetal growth and PVE and fetal growth and GFR. Thus, a new, well-designed and adequately powered study would be likely to change

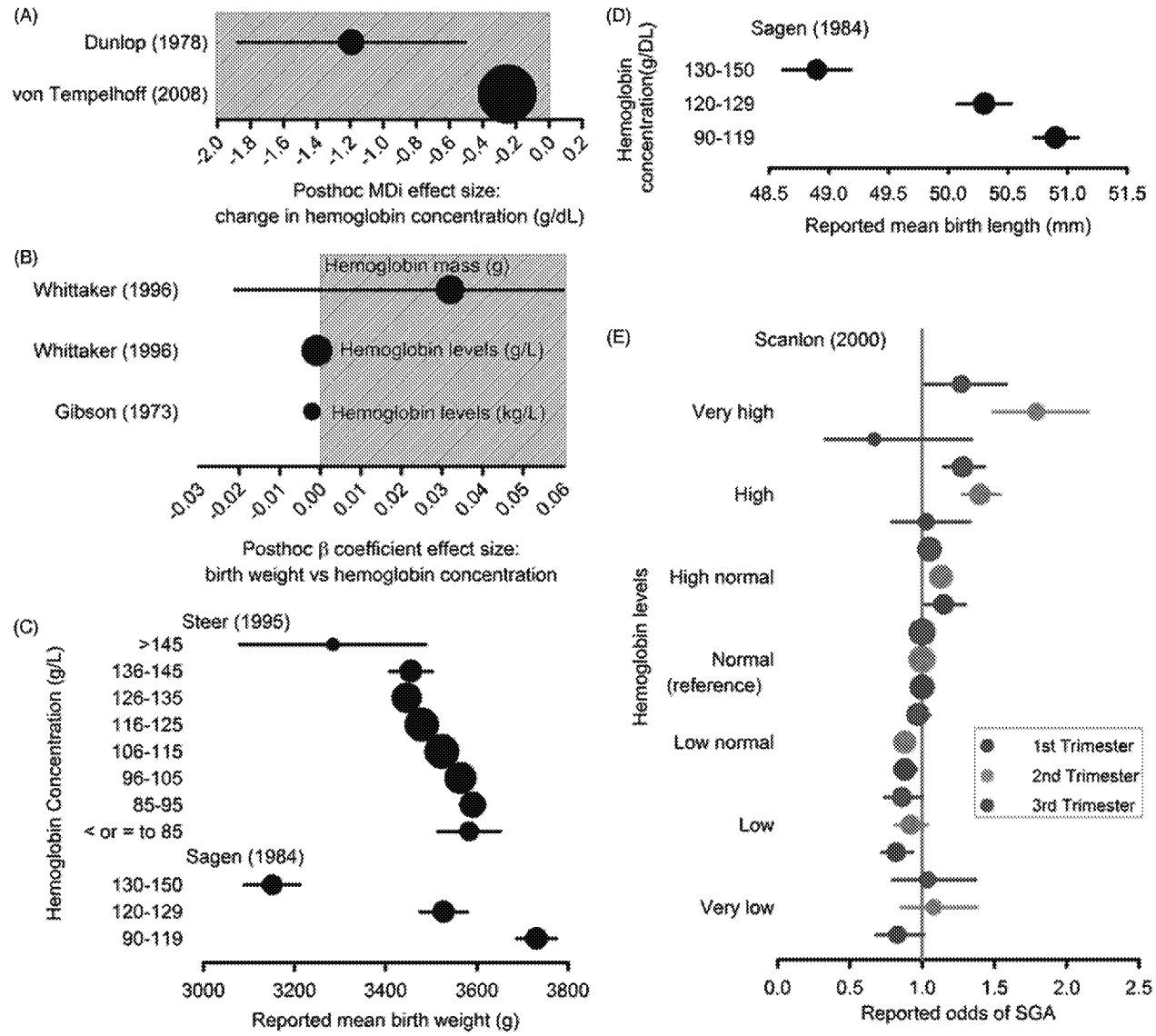

Figure 2. Association between fetal growth and hemoglobin levels. (A) *Post-hoc* mean difference effect sizes for the change in hemoglobin concentration in women gave birth to higher versus lower birth weight babies; (B) *post-hoc* beta-coefficients for the association between mean birth weight and hemoglobin levels; (C and D) reported data on the association between mean birth weight for various stratifications of hemoglobin; (E) reported odds of SGA for various stratifications of hemoglobin levels. Horizontal error bars represent 95% CI and symbol sizes represent the log of the number of study participants. For graphs of *post-hoc* calculated effect sizes, the shaded area represents the direction of effect (positive or negative in relation to zero (no effect)) which is consistent with the hypotheses for the change in normal pregnancy as outlined in Supplementary Material 1.

the certainty in the direction and strength of effect for all three relationships in the model.

- Our rationale for ''inadequate'' evidence of an association from experimental mammalian studies was based on the ''very low'' quality of evidence and a lack of confidence in the effect because the data were limited in both size and number. One study was designed to assess the direction of effect (causality) between fetal growth and PVE [15], with the results suggesting that fetal growth restriction preceded a decrease in plasma volume; however, this study was both small and of low quality. There was insufficient evidence on the other relationships in the model to assess the direction of effect between fetal growth and GFR, either directly or via change in PVE. Thus, a new, well-designed and adequately powered study would be likely to change the certainty in the direction and strength of the effect.

Integrating the evidence across evidence streams

The final step in our review was to integrate the strength ratings from the human and non-human evidence streams to determine the strength of the evidence over all. We found that the association between fetal growth and GFR was ''not classifiable'' (Figure 3) based on ''inadequate'' human evidence.

Discussion

To our knowledge this is the first systematic review on the strength of the evidence for a relationship between fetal growth and GFR. We found that the strength of the evidence for an association between fetal growth and GFR is ''not classifiable'' based on inadequate human and inadequate non-human evidence. Our findings systematically and transparently document that there is currently no empirical evidence

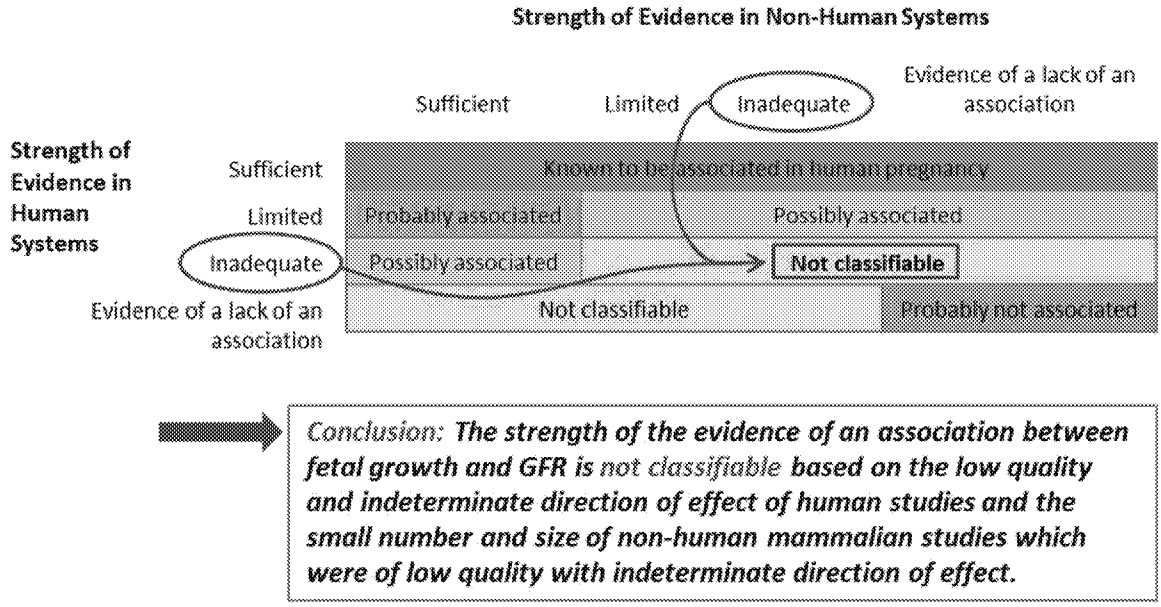

Figure 3. Overview of the framework to integrate strength of evidence from the human and non-human evidence streams to reach a conclusion on the strength of the association between fetal growth and GFR.

to support the hypothesis, but the findings do not disprove the reverse causality hypothesis. A well-conducted observational human study could increase our confidence in the strength of the association between the three variables (FG, PVE, GFR), and a well-conducted experimental mammalian study could increase our confidence in the direction of effect.

We found that the strength of the evidence differed among the various direct and indirect potential relationships considered. We found sufficient evidence of a relationship between birth weight and PVE from human studies (based on data from two large studies with low risk of bias [13,14] and reasonably consistent data from the small studies), an inconsistent effect between fetal growth and GFR, and insufficient data to assess the relationship between PVE and GFR. Moreover, for all three relationships examined, the direction of effect could not be determined. Despite one experimental study [15] suggesting that fetal growth could impact PVE, the size and quality of this study was insufficient to alter our conclusions. Assessing associations from observational studies is challenging; however, a high quality, well-designed and adequately-powered, experimental mammalian study using directly-relevant endpoints would give us greater confidence in both the strength and direction of the effect.

Limitations

Although we have used a systematic and transparent method to address our study question, there are a number of limitations to our approach. First, systematic reviews can only include studies which are available in the public domain, or which have been made available through, for example, contacting authors, which we did not do in this systematic review due to time constraints. Therefore, it cannot be ruled out that our review was missing studies that could have influenced the outcome. It should be noted that we were unable to locate one article despite a broad interlibrary loan search and attempts to contact the authors; however, we determined from the abstract that the article was on the relationship between fetal growth and PVE from 32 pregnant women [16], which we considered unlikely to alter our conclusions due to its small size.

Secondly, in our *post-hoc* findings we cannot rule out the possibility of spurious findings. Where we calculated difference in means effect sizes we took 95% CIs which did not cross zero as significant results at $p<0.05$ and thus we were unable to make adjustments for multiple comparisons as we did not formally calculate a p value [17].

Lastly, while the process that we have used is transparent, the conclusions on the quality and strength of the evidence involved judgments, which in turn can depend on the composition and interactions among study authors. It is possible that a different group of researchers at a different time might reach a different conclusion. The raw material used for our decision is available to the public so that any disagreement in our judgment can be openly discussed.

Summary and conclusions

We conducted a systematic review of the evidence of an association between fetal growth and GFR in order to assess the strength of the evidence of a ''reverse causality'' hypothesis, a potential alternate explanation for any body of observational studies that documents an inverse association between prenatal exposure to chemicals cleared renally and fetal growth. Using pre-specified factors, we found the quality of observational human and non-human studies to be ''low,'' and experimental non-human studies to be ''very low.'' We considered the overall strength of all three streams of evidence to be ''inadequate'' according to pre-specified and transparent definitions. We found evidence of an association between fetal growth and PVE; however, the small number, size and quality of the studies on GFR did not permit a conclusion on the association between fetal growth and GFR, either directly or via change in PVE. Moreover, we found insufficient data to perform a meta-analysis on any of the three relationships assessed. Finally, we used The Navigation

Guide methodology to integrate our strength ratings from human and non-human evidence streams and found the strength of the evidence on the association between fetal growth and GFR to be ''not classifiable''. At present, there is insufficient evidence to reliably assess whether the ''reverse causality'' hypothesis could explain the observed inverse association between exposure to chemicals and fetal growth. Further investigation of this hypothesis in high quality, well designed and adequately powered human and non-human studies are needed in order to reach a conclusion on the association between fetal growth and GFR.

Acknowledgements

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Declaration of interest

The authors have no conflicts of interest to declare.

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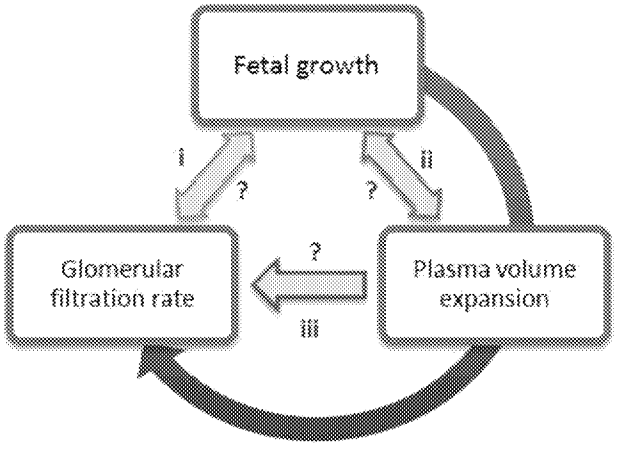
Supplementary Figure 1. A schematic of the three relationships we assessed to draw a conclusion on the strength of the association between fetal growth and GFRa. We considered both the direct evidence (A, arrow i) and the indirect evidence via PVE, by assessing the relationship between fetal growth and PVE (A, arrow ii), and PVE and GFR (A, arrow iii)b. Additionally we always considered variables downstream on the circular grey arrow to be the dependent variable in post-hoc analyses of study data, as outlined in the table (B).

A.



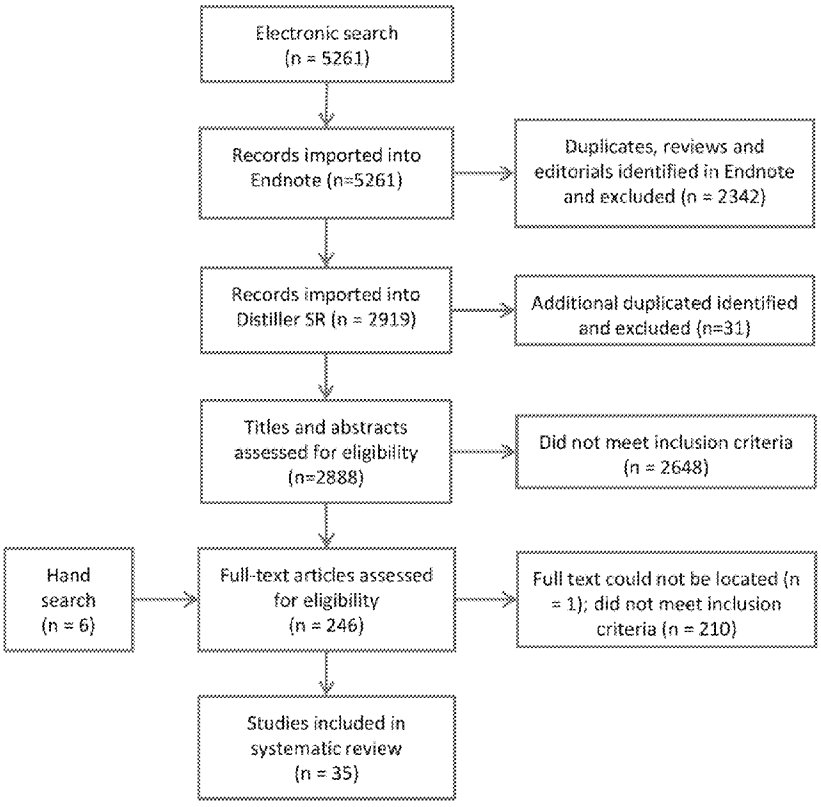
B.

	Independent variable:		Dependent Variable: Outcome
	"Exposure"	Comparator	
i.	Higher value for fetal growth	Lower value for fetal growth	Δ GFR
ii.	Higher value for fetal growth	Lower value for fetal growth	Δ PVE
iii.	Higher value for PVE	Lower value for PVE	Δ GFR

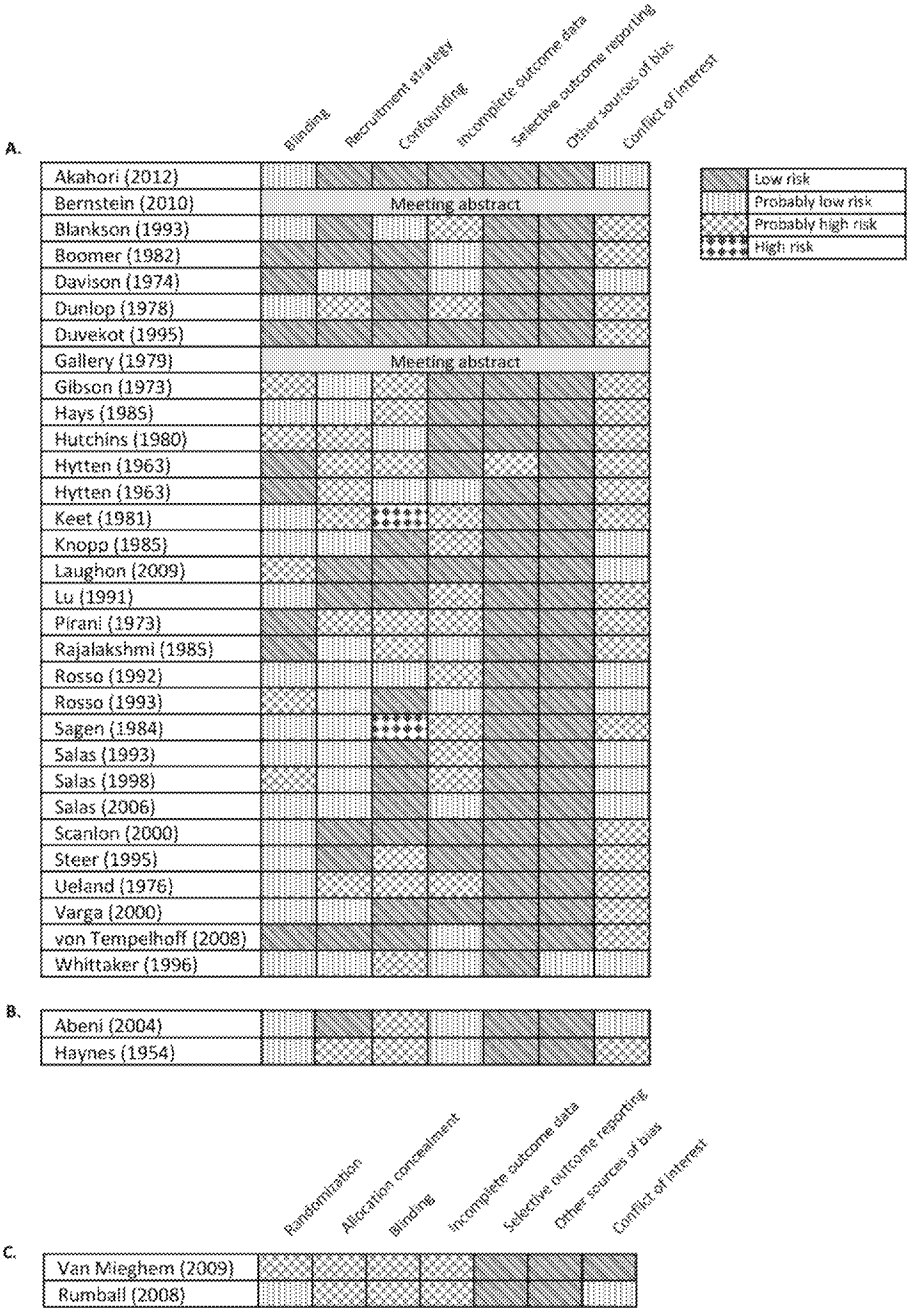
[a] We adapted our method from The Navigation Guide [6] which describes steps to review the association between exposure to potentially toxic chemicals and adverse health outcomes; we therefore interchanged the term 'exposure' in the Navigation Guide with higher and lower values for fetal growth or PVE.

[b] Color scheme corresponds to the relationships shown in Table 4.

Supplementary Figure 2. Results of selecting the evidence included in this review (n=35 studies).

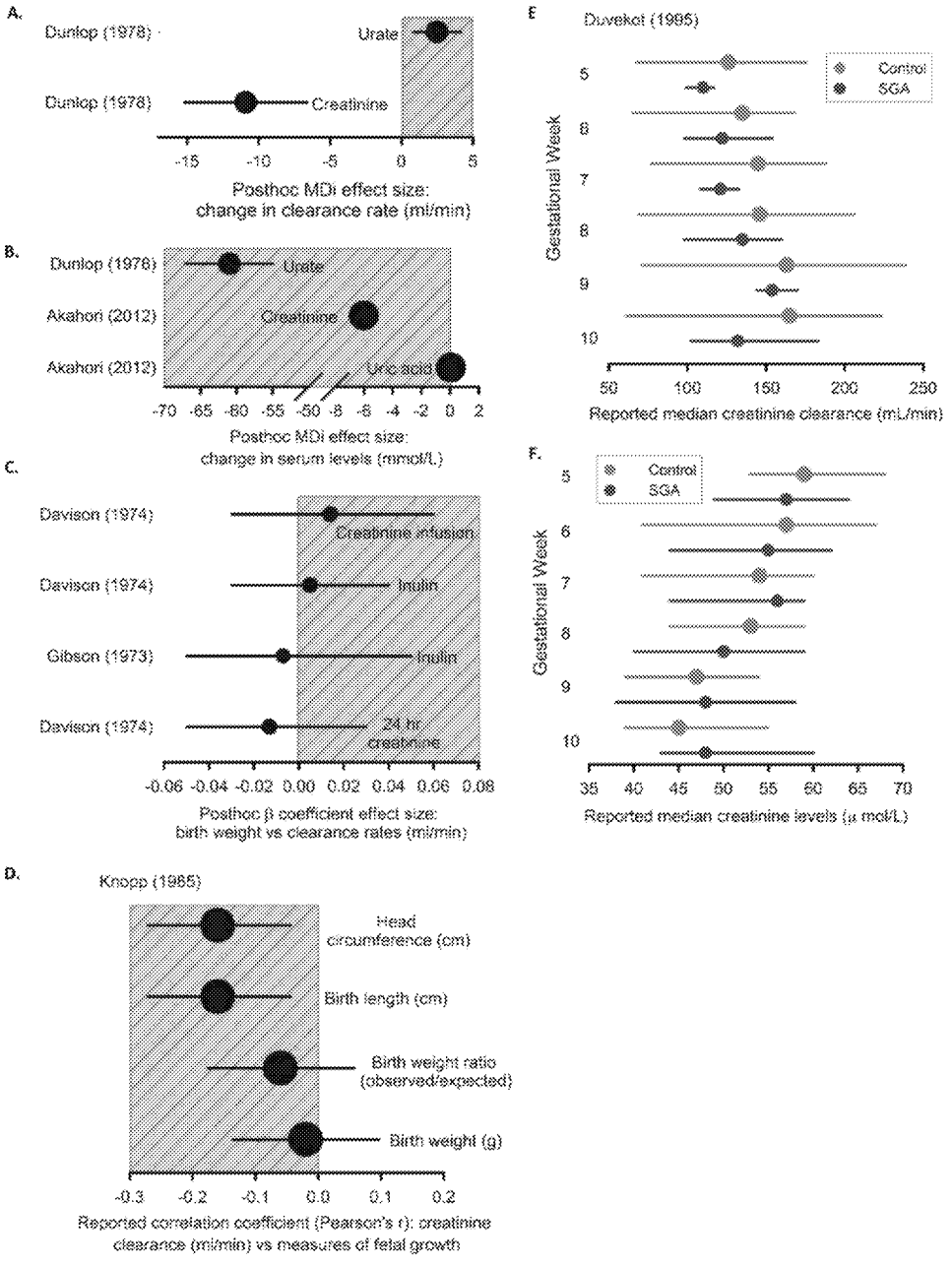


Supplementary Figure 3. Risk of bias assessment across individual studies. (A) Observational human studies, (B) observational mammalian studies, and (C) experimental mammalian studies were rated as low risk, probably low risk, probably high risk or high risk for seven risk of bias domains[a].

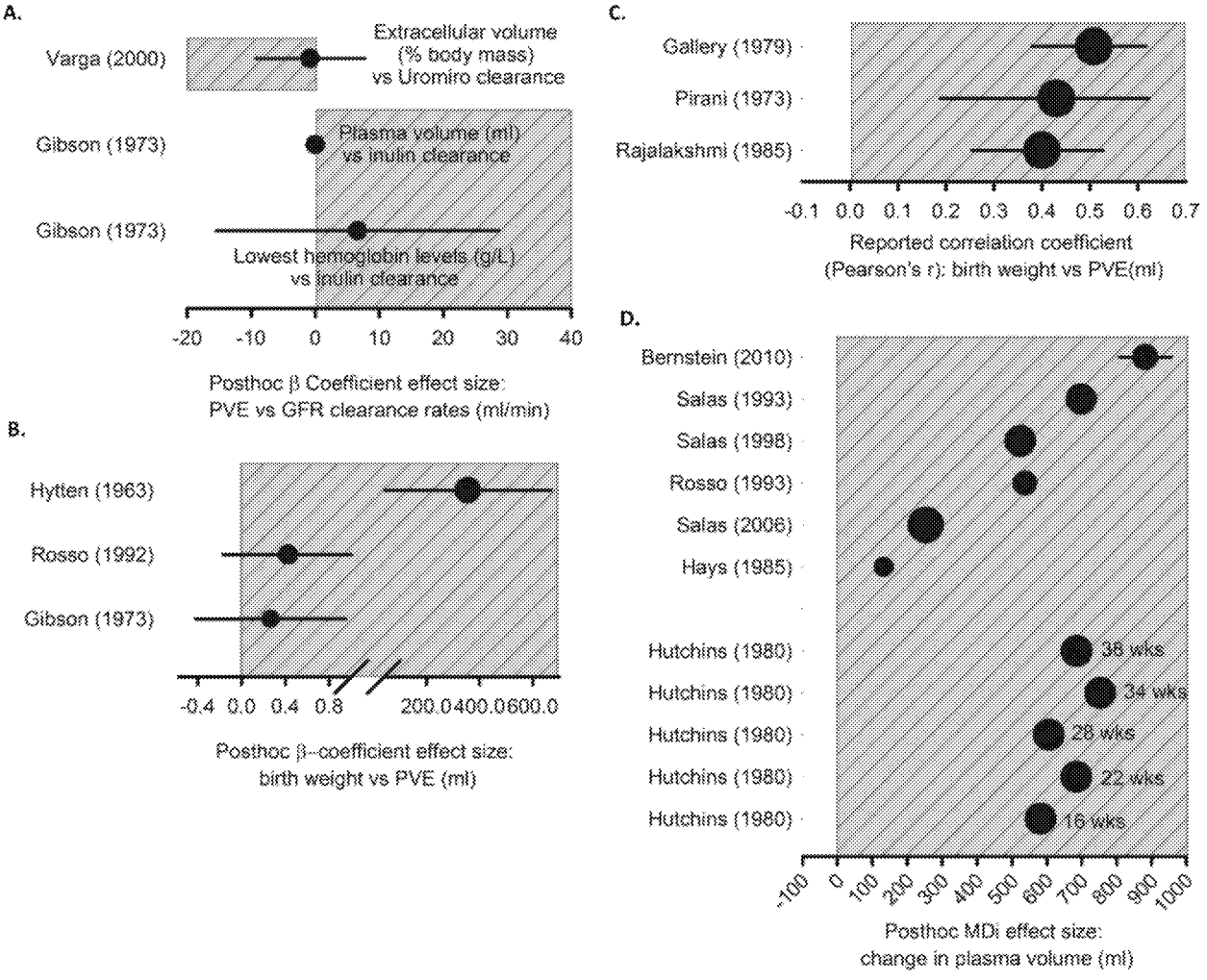


[a]Dark green diagonal stripes, low risk of bias; light green vertical stripes, probably low risk of bias; pink squares, probably high risk of bias; and red diamonds, high risk of bias.

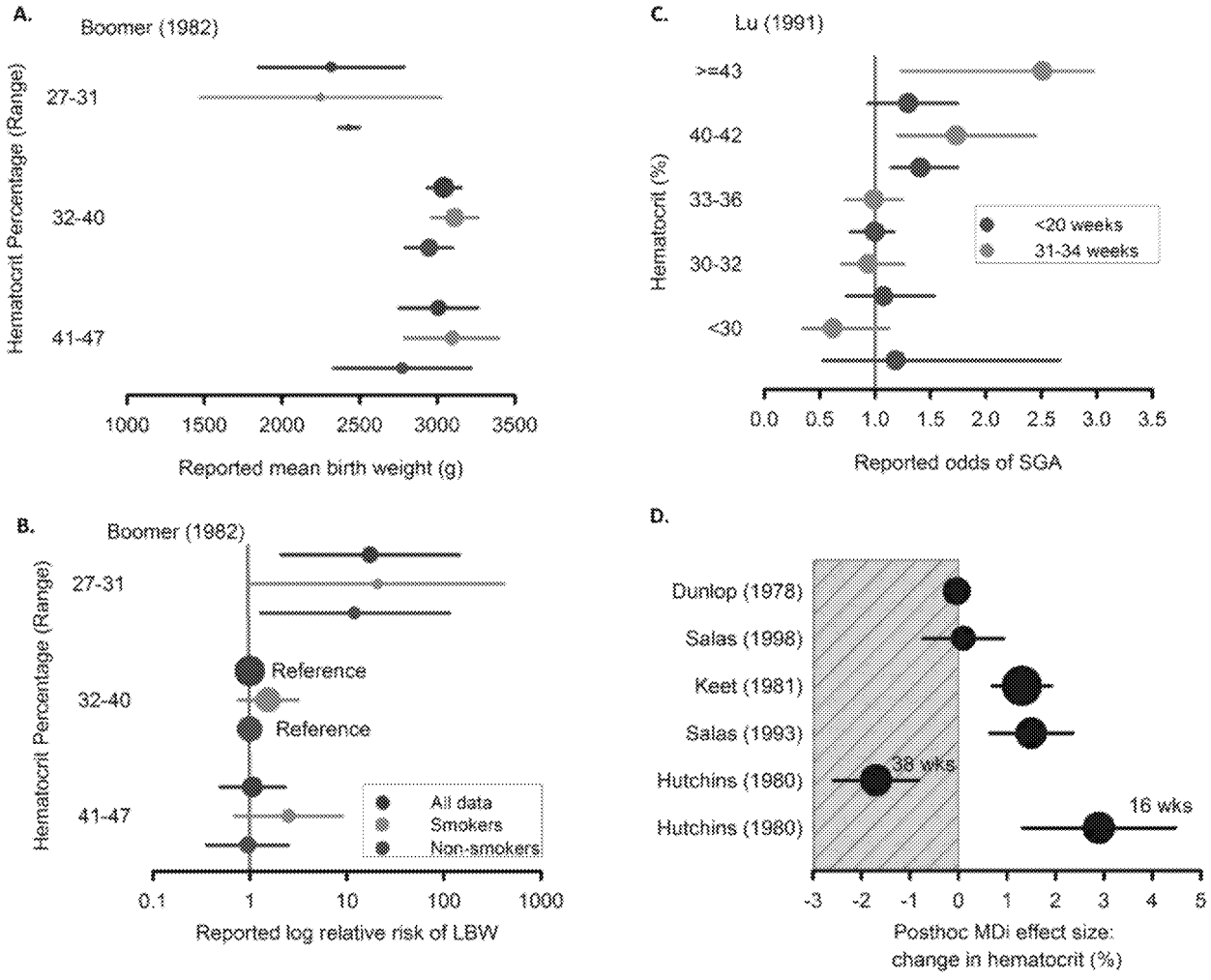
Supplementary Figure 4. Association between fetal growth and GFR. (A and B) post-hoc mean difference effect sizes for change in clearance rate (A) and serum levels (B) of biomarkers indicative of GFR in women who gave birth to higher versus lower birth weight babies; (C) post-hoc beta-coefficients from regression analyses on the association between increased birth weight and change in clearance rates; (D) reported correlation coefficients for the association between creatinine clearance and measures of fetal growth; (E and F) reported medians and ranges for creatinine clearance (E) and creatinine levels (F) at various gestational ages. Horizontal error bars represent 95% CI and symbol sizes represent the log of the number of study participants. For graphs of post-hoc calculated effect sizes, the shaded green area represents the direction of effect (positive or negative in relation to zero (no effect)) which is consistent with the hypotheses for the change in normal pregnancy as outlined in Table 1.



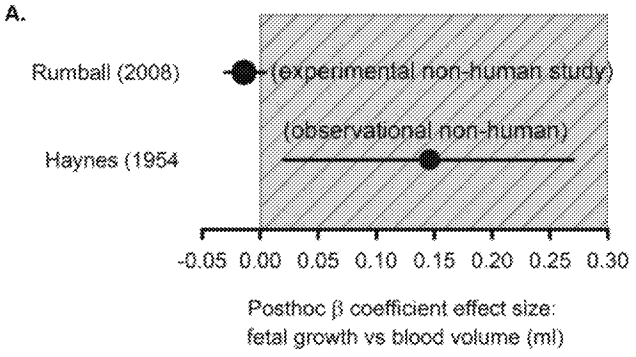
Supplementary Figure 5. Associations between PVE and fetal growth or GFR. (A and B) Posthoc beta-coefficients from regression analyses of individual participant data on the association between (A) change in markers of PVE and GFR clearance and (B) birth weight and PVE; (C) reported correlation coefficients for the relationship between PVE and birth weight; and (D) post-hoc mean difference effect sizes for the change in plasma volume in women gave birth to control versus lower birth weight babies. Horizontal error bars represent 95% CI and symbol sizes represent the log of the number of study participants. For graphs of post-hoc calculated effect sizes, the shaded green area represents the direction of effect (positive or negative in relation to zero (no effect)) which is consistent with the hypotheses for the change in normal pregnancy as outlined in Table 1.

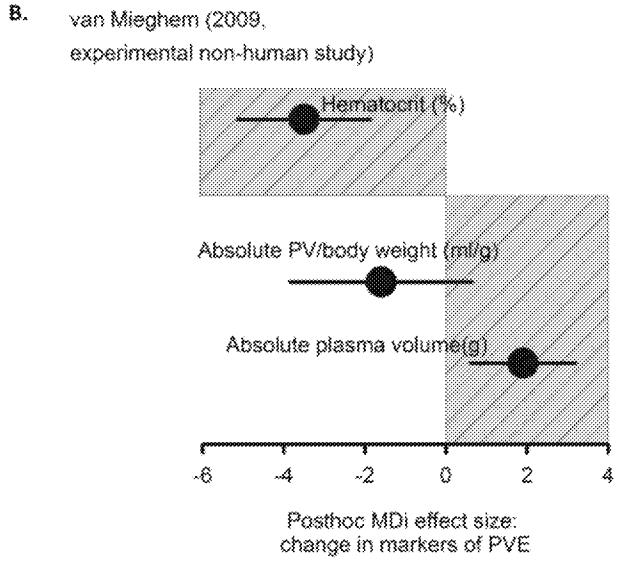


Supplementary Figure 6. Association between fetal growth and hematocrit percentage. (A) Reported data on the mean birth weight, (B) reported relative risk of low birth weight and (C) reported odds of SGA for stratifications of hematocrit; and (D) post-hoc mean difference effect sizes for change in hematocrit measured in women who gave birth to higher versus lower birth weight babies. Horizontal error bars represent 95% CI and symbol sizes represent the log of the number of study participants. For the graph of post-hoc calculated effect sizes (D), the shaded green area represents the direction of effect (positive or negative in relation to zero (no effect)) which is consistent with the hypotheses for the change in normal pregnancy as outlined in Table 1.



Supplementary Figure 7. Association between fetal growth and PVE in non-human studies. (A) Post-hoc mean difference effect sizes for hematocrit percentage and absolute plasma volume, both adjusted and unadjusted for maternal weight; (B) post-hoc beta coefficients for the association between fetal growth and blood volume. Horizontal error bars represent 95% CI and symbol sizes represent the log of the number of study participants. The shaded green area represents the direction of effect (positive or negative in relation to zero (no effect)) which is consistent with the hypotheses for the change in normal pregnancy as outlined in Table 4.





Supplementary material 1. Specific outcome measures we extracted data for and their typical change during normal, uncomplicated pregnancy compared to non-pregnant women[1].

Variable	Outcome Measures	Change during pregnancy
PVE	Plasma volume expansion	Increases
	Absolute plasma volume	
	Blood volume or uterine blood volume	
	Plasma volume increment	
	Extracellular volume	
	Lowest hemoglobin levels	Lower levels associated with greater PVE
	Hemoglobin levels or concentration	Decreases
	Hemoglobin mass	
	Hematocrit percentage	
GFR	Clearance of creatinine, uric acid, inulin, Uromiro or urate	Increases
	Levels or concentration of creatinine, uric acid, inulin or serum	Decreases

Supplemenatary Material 2. The "PECO" aid to outline the study question.

Participants: Humans or other mammals without adverse health conditions studied at any stage during or until the end of pregnancy.

Exposure: In the Navigation Guide method, 'exposure' is considered the environmental agent of interest. In applying the method to our question, we designated 'exposure' to be the independent variable of interest, e.g. fetal growth (Figure 1B). For studies where change in fetal growth and any other variable (e.g., PVE) was assessed, exposure groups were those with higher levels of fetal growth (see data evaluation section below) relative to the comparator group; for studies where change in maternal PVE and maternal GFR was assessed, exposure groups were those with higher levels of PVE relative to the comparator group.

Comparator: For studies where change in fetal growth and any other variable was assessed, comparator groups were those with lower levels of fetal growth relative to the exposure group; for those studies where change in maternal PVE and maternal GFR was assessed, comparator groups were those with lower levels of PVE relative to the exposure group (Figure 1B).

Outcome: For studies where fetal growth and maternal PVE were assessed, the outcome was change in maternal PVE; for those where fetal growth and maternal GFR was assessed, the outcome was change in maternal GFR (Figure 1B). In addition, we considered any suitable measures of maternal GFR (e.g. inulin or creatinine clearance), fetal growth (e.g. birth weight, head circumference), and PVE (e.g. hemodilution or blood volume expansion) (Supplementary Material 1). We also included absolute plasma or blood volume as surrogate markers for PVE if maternal size was either sufficiently similar between the exposure and comparator group (e.g. statistical non-significance) or adjusted for in the analysis.

Supplementary Material 3. A summary of the individual relationships assessed in each publication included the systematic review on the association between fetal growth and GFR[a].

	First author, year [citation]	Sample Size	Relationship	Post-hoc Data Analysis	For presented results see:
Observational Human Studies	Akahori, 2012 [2]	120	Fetal growth and GFR	Mdi	Fig. S4B
	Davison, 1974 [3]	10		Regression	Fig. S4C
	Dunlop, 1978 [4]	34		Mdi	Fig. S4A & B
	Duvekot,1995 [5]	24		None	Fig. S4E & F
	Gibson, 1973 [6]	9		Regression	Fig. S4C
	Knopp, 1985 [7]	283		None	Fig. S4D
	Laughon, 2009 [8]	212		None	Table 5 (row 1a)
	Bernstein, 2010 [9], Abstract	29	Fetal growth and PVE	Mdi	Fig. S7D
	Blankson, 1993 [10]	17,149[b]		None	Table 5 (row 1b)
	Boomer, 1985 [11]	633		None	Fig. S6A & B
	Dunlop,1978 [4]	34		Mdi	Fig. S6D & M2A
	Gallery. 1979 [12], Abstract	150		None	Fig. S7C
	Gibson, 1973 [6]	9		Regression	Fig. S5B & M2B
	Hays, 1985 [13]	12		Mdi	Fig. S5D
	Hutchins, 1980 [14]	60		Mdi	Fig. S5D & 6D
	Hytten, 1963 [15]	109		Regression	Fig. S5B
	Hytten, 1963 [16]	39		None	Table 5 (row 1c)
	Keet, 1981 [17]	185		Mdi	Fig. S6D
	Lu, 1991[18]	17,149[b]		None	Fig. S6C
	Pirani, 1973 [19]	56		None	Fig. S5C
	Rajalakshmi, 1985 [20]	145		None	Fig. S5C
	Rosso, 1992 [21]	12		Regression	Fig. S5B
	Rosso, 1993 [22]	22		Mdi	Fig. S5D
	Sagen, 1984 [23]	877		None	Fig. M2C & D
	Salas, 1993 [24]	56		Mdi	Fig. S5D & 6D
	Salas, 1998 [25]	62		Mdi	Fig. S5D
	Salas, 2006 [26]	118		Mdi	Fig. S5D & S6D
	Scanlon, 2000 [27]	173,031		None	Fig. M2E
	Steer, 1995 [28]	157,996		None	Fig. M2C
	Ueland, 1976 [29]	75		None	Table 5 (row 1c)
	von Tempelhoff, 2008 [30]	4432		Mdi	Fig. M2B
	Whittaker, 1996 [31]	68		Regression	Fig. M2B
	Gibson, 1973 [6]	9	PVE and GFR	Regression	Fig. S5A
	Varga, 2000 [32]	11		Regression	Fig. S5A
Obs. Mam	Abeni, 2004 [33]	59 Cows	Fetal growth and GFR	None	Table 5 (row 2)
	Haynes, 1954 [34]	6 Dogs	Fetal growth and PVE	Regression	Fig. S7B
Exp. Mam	Rumball, 2008 [35]	9 Ewes	Fetal growth and PVE	Regression	Fig. S7B
	Van Mieghem, 2009 [36]	17 Rats		Mdi	Fig. S7A

[a] Abbreviations: Mdi, difference in means effect size; Exp. Mam, experimental mammalian studies; Obs. Mam, observational mammalian studies.

[b] Same study population.

Supplementary Material 4: A summary of findings from the observational human studies included in the systematic review[1].

1b. Birth weight vs GFR biomarkers (clearance rate; hypothesis: clearance rate increases with increasing birth weight).						
Reference	**Exposure/ Comparator**	**Outcomes**	**N**	**Effect Size (95% CI)**	**Summary**	**Fig.**
Dunlop (1978)	Control (details unknown), n=25 VS LBW (details unknown), n=9	Creatinine clearance (ml/min)	34	MDi: 10.9 ml/min decrease in the higher birth weight group (6.62 to 15.2)	Greater creatinine clearance in the low birth weight group, although in the original study the authors did not identify a significant difference.	S4A
Dunlop (1978)	Control (details unknown), n=25 VS LBW (details unknown), n=9	Urate clearance (ml/min)	34	MDi: 2.48 ml/min increase in the higher birth weight group (0.81 to 4.15)	Greater urate clearance in the higher birth weight group. In the original study the authors did not identify a significant difference.	S4A
Davison (1974)	Birth weight (g)	Creatinine clearance, infusion (ml/min)	10	β: 0.014 (-0.03 to 0.06); adj R2=<0; p=0.464	Increasing creatinine clearance with increasing birth weight, although not a significant result.	S4B
	Birth weight (g)	Creatinine clearance, 24 hours (ml/min)	10	β: -0.013 (-0.05 to 0.03); adj R2=<0; p=0.495	Decreasing creatinine clearance with increasing birth weight, although not a significant result.	S4B
	Birth weight (g)	Inulin clearance (ml/min)	10	β: 0.005 (-0.03 to 0.04); adj R2=<0; p=0.759	Increasing inulin clearance with increasing birth weight, although not a significant result.	S4B
Gibson (1973)[b]	Birth weight (g)	Inulin clearance (ml/min)	9	β: -.007 (-0.05 to 0.04); adj R2=<0; p=0.704	Decreasing creatinine clearance with increasing birth weight, although not a significant result.	S4C
Duvekot (1995)	Birth weight, stratified into control and LBW (<10th percentile).	24 hours creatinine clearance (mL/min), continuous variable.	24	N/A. Author summary: the authors did not report a significant difference in creatinine clearance in early pregnancy between women who delivered low birth weight or average birth weight babies.	We did not perform a post-hoc analysis because data are presented as medians and ranges.	S4F
1a. Birth weight vs GFR biomarkers (serum levels or concentration; hypothesis: serum levels or concentration decrease with increasing birth weight).						
Reference	**Exposure/ Comparator**	**Outcomes**	**N**	**Effect Size (95% CI)**	**Summary**	**Fig.**
Akahori (2012)	Control (>10th AND <90th percentile), n=80 VS LBW (<10th percentile), n=40	Creatinine levels (μ mol/l)	120	MDi: 6.0 μ mol/l decrease in the higher birth weight group (5.0 to 7.0)	Decrease in creatinine levels the higher birth weight group.	S4B
		Uric acid levels (mmol/l)	120	MDi: 0.05 mmol/l decrease in the higher birth weight group (-0.04 to 0.14)	Decrease in uric acid in the higher birth weight group, although not significant; study authors did find a significant difference (p=0.0003).	S4B
Dunlop (1978)	control (details unknown), n=25 VS LBW (details unknown), n=9	Serum urate concentration (μ mol/l)	34	MDi: 61 μ mol/l decrease in the higher birth weight group (54.9 to 67.1)	Decrease in the higher birth weight group.	S4B
Duvekot (1995)	Birth weight, stratified into control and LBW (<10th percentile).	Creatinine levels (micro mol/L) and 24 hours creatinine clearance (mL/min), continuous variables.	24	N/A. Author summary: The authors did not report a significant difference in creatinine levels between women who delivered low birth weight or average birth weight babies.	We did not perform a post-hoc analysis because data are presented as medians and ranges.	S4E

[1] Abbreviations: LBW, low birth weight; MDi, difference in means effect size.

Knopp (1985)	Birth weight, birth weight ratio, birth length and head circumference, all continuous outcomes.	Serum creatinine concentration, continuous outcome.	283	N/A. Author summary: Significant, inverse relationship with birth weight (r=-0.16, p<0.01), birth weight ratio (r=-0.16, p<0.01); no association with birth length (rho=-0.06, NS), and head circumference (rho=-0.02, NS; n=283).	We did not perform a post-hoc analysis because data are presented as correlation coefficients.	S4D
Laughon (2009)	Odds of SGA	Uric acid concentration, continuous variable and stratified.	212	N/A. Author summary: "SGA occurred in 30.8% of pregnancies in normotensive women with uric acid in the highest quartile (uric acid >4.1 mg/dL) compared with only 3.4% of normotensive women with uric acid in the lowest quartile (uric acid ≤2.9 mg/dL; P<.001). Uric acid concentrations as a continuous measure were associated with SGA in normotensive women after adjusting for maternal pre-pregnancy BMI and race (odds ratio, 1.06; 95% CI, 1.01–1.12; P <.02). When additionally adjusted for smoking, the magnitude of the association was unaffected, but precision was compromised (odds ratio, 1.05; 95% CI, 0.99 –1.10; P<.09). Uric acid was weakly correlated with smoking (r=0.14; p<.03)."	We did not perform a post-hoc analysis because the data presentation did not permit an effect size calculation or regression analysis.	N/A

2a. Birth weight vs PV (expansion, increment or absolute; hypothesis: plasma volume increases with increasing birth weight).

Reference	Exposure/ Comparator	Outcomes	N	Effect Size (95% CI)	Summary	Fig.
Bernstein (2010), Abstract.	Control (no information given), n=27 VS IUGR (<5th percentile), n=2	PVE (mL)	29	MDi: 881.5 mL increase in the higher birth weight group (807.82 to 955.18)	Greater PVE in the higher birth weight group	S5D
Hays (1985)	Control (>10th percentile), n=9 VS LBW (<10th percentile), n=3	Absolute PV (mL/m³)	12	MDi: 83 mL/m² increase in the higher birth weight group (64.9 to 101.1)	Greater PV in the higher birth weight group	S5D
Hutchins (1980)	European, n=30 (birth weight 3049 g +- 31 SE) VS Indian, n=30 (birth weight 2804 g +- 504 SE)	Absolute PV (mL/kg) at 16 wks	60	MDi: 0.73 mL/kg increase in the higher birth weight group (-0.65 to 2.11)	Greater PV in the higher birth weight group; significantly greater absolute plasma volume in the higher birth weight group at 22, 28, 34 and 38 weeks; the authors found a statistical difference at all time points.	S5D
		Absolute PV (mL/kg) at 22 wks	60	MDi: 2.11 mL/kg increase in the higher birth weight group (0.62 to 3.6)		
		Absolute PV (mL/kg) at 28 wks	60	MDi: 0.36 mL/kg increase in the higher birth weight group (-1.17 to 1.89)		
		Absolute PV (mL/kg) at 34 wks	60	MDi: 2.94 mL/kg increase in the higher birth weight group (1.34 to 4.54)		
		Absolute PV (mL/kg) at 38 wks	60	MDi: 2.35 mL/kg increase in the higher birth weight group (0.95 to 3.75)		
Rosso (1993)	Control (>10th percentile), n=11 VS LBW (<10th percentile), n=11	Absolute PV (mL)	22	MDi: 537 mL increase in the higher birth weight group (521.13 to 552.87)	Greater PV in the higher birth weight group	S5D
Salas (1993)	Control (>10th percentile), n=26 VS LBW (<10th percentile); n=30	PVE (mL)	56	MDi: 698 mL increase in the higher birth weight group (682.94 to 713.06)	Greater PVE in the higher birth weight group	S5D

Salas (1998)	Control (>10th percentile), n=37 VS LBW (<10th percentile), n=25	Absolute PV (mL)	62	MDi: 524 mL increase in the higher birth weight group (512.73 to 535.27)	Greater PV in the higher birth weight group	S5D
Salas (2006)	Control (>10th percentile), n=95 VS LBW (<10th percentile), n=23	Absolute PV (mL)	118	MDi: 253 mL increase in the higher birth weight group (245.02 to 260.98)	Greater PV in the higher birth weight group	S5D
Gibson (1973)[b]	Birth weight (g)	PV increment (mL)	9	β: 0.264 (-0.42 to 0.95); adj R2=<0; p=0.391; n=9	Increasing PV increment with increasing birth weight but not a significant relationship.	S5B
Hytten (1963a)	Birth weight (g)	PVE (mL)	28	β: 355.5 (43.6 to 667.4); adj R2=0.12; p=0.027; n=28	Increasing PVE with increasing birth weight.	S5B
Rosso (1992)	Birth weight (g)	Absolute PV (mL)	12	β: 0.424 (-0.17 to 1.02); adj R2=0.12; p=0.143; n=12	Increasing PV with increasing birth weight but not a significant relationship.	S5B
Rajalakshmi (1985)	Birth weight, stratified into control (>2500g) and LBW (<2500g) or continuous variable.	Plasma volume (ml and ml/kg), continuous variables.	145	N/A. Author summary: Significant correlation between absolute plasma volume and birth weight (r=0.3996, p<0.02). Specifically, plasma volume was significantly lower in the low birth weight group (2564+-253 SD) compared to the normal birth weight group (3033+-467 SD; p<0.001).	We did not perform a post-hoc analysis because data are presented as correlation coefficients or mean scores in two birth weight groups. We were unable to perform any post-hoc analyses because sample sizes per group were not reported.	S5C
Gallery (1979), Abstract	Birth weight, continuous variable.	PVE, continuous variable	150	N/A. Author summary: Significant positive correlation between plasma volume expansion at 22-36 weeks and birth weight (r=0.508, p<0.001).	We did not perform a post-hoc analysis because data are presented as correlation coefficients. Meeting abstract.	S5C
Pirani (1973)	Birth weight, continuous variable.	Plasma volume (ml), continuous variable.	56	N/A. Author summary: Significant relationship between plasma volume expansion and birth weight (r = 0.43; y=0.275x + 2250.6, p<0.01, n=56).	We did not perform a post-hoc analysis because data are presented as correlation coefficients. Sample sizes per group are not reported.	S5C
2b. Birth weight vs hematocrit (hypothesis: hematocrit decreases with increasing birth weight).						
Reference	**Exposure/ Comparator**	**Outcomes**	**N**	**Effect Size (95% CI)**	**Summary**	**Fig.**
Blankson (1993)	Odds of IUGR	Hematocrit, stratified into six groups.	17,149	N/A. Author summary: Significantly increased odds of SGA for some comparisons (between 40-42% in black and white women in early pregnancy and hematocrit >40% in white women in late pregnancy).	We did not perform a post-hoc analysis because sample sizes per group are not reported and the data presentation did not permit an effect size calculation or regression analysis.	N/A
Boomer (1982)	Birth weight, continuous variable	Hematocrit, stratified into three groups	633	N/A. Birth weight was significantly lighter in the low hematocrit group (N=201, p<0.05) and smokers in the higher hematocrit groups gave birth to lighter babies although the difference was not significant. The relative risk of LBW was also significantly greater in the low hematocrit group (N=63, p<0.01). The relative risk was higher for both smokers and non-smokers in the low hematocrit group (p<0.01). The authors conclude that the association between low birth weight and low hematocrit occurs irrespective of maternal smoking.	We did not perform a post-hoc analysis because the data presentation did not permit an effect size calculation or regression analysis.	S6A &B

Hutchins (1980)	European, n=30 (birth weight 3049 g +- 31 SE) VS Indian, n=30 (birth weight 2804 g +- 504 SE)	Hematocrit (%) at 16 wks	60	MDi: 2.9% increase in the higher birth weight group (1.33 to 4.47)	Greater hematocrit in the higher birth weight group at 16 weeks and in the lower birth weight group at 38 weeks. The authors did not find a statistical difference.	S6D
		Hematocrit (%) at 28 wks	60	MDi: 1.7% decrease in the higher birth weight group (0.82 to 2.58)		
Dunlop (1978)	control (details unknown), n=25 VS LBW (details unknown), n=9	Hematocrit (%), unknown time of assessment	34	MDi: 0.03% decrease in the higher birth weight group (-0.09 to 0.15)	Greater hematocrit in the lower birth weight group.	S6D
Keet (1981)	Control (>10th percentile), n=112 VS LBW (<10th percentile), n=73	Hematocrit (%), unknown time of assessment	185	MDi: 1.31% increase in the higher birth weight group (0.70 to 1.92)	Greater hematocrit in the higher birth weight group.	S6D
Lu (1991)	Odds of SGA	Hematocrit, stratified into four groups.	17,149	N/A. Author summary: Significantly increased odds of SGA for some stratifications of hematocrit in unadjusted analyses (>40% at <20 weeks and between 31-40 weeks gestation; >43% at 26-30 weeks gestation) and in adjusted, multivariate analyses (40-42% at <20 weeks and >40% at 31-34 weeks gestation, $p<0.05$). No other significant associations.	We did not perform a post-hoc analysis because sample sizes per group are not reported and the data presentation did not permit an effect size calculation or regression analysis.	S6C
Salas (1993)	Control (>10th percentile), n=26 VS LBW (<10th percentile); n=30	Hematocrit (%) at 30-34 wks	56	MDi: 1.5% increase in the higher birth weight group (0.64 to 2.36)	Greater hematocrit in the higher birth weight group.	S6D
Salas (1998)	Control (>10th percentile), n=37 VS LBW (<10th percentile), n=25	Hematocrit (%), unknown time of assessment	62	MDi: 0.1% increase in the higher birth weight group (-0.73 to 0.93)	Greater hematocrit in the higher birth weight group.	S6D
2c. Birth weight vs hemoglobin levels (hypothesis: hemoglobin levels decrease with increasing birth weight).						
Reference	**Exposure/ Comparator**	**Outcomes**	**N**	**Effect Size (95% CI)**	**Summary**	**Fig.**
Dunlop (1978)	control (details unknown), n=25 VS LBW (details unknown), n=9	Hemoglobin (g/dL), unknown time of assessment	34	MDi: 1.19 g/dL decrease in the higher birth weight group (0.5 to 1.88)	Greater hemoglobin levels in the lower birth weight group.	S6B
Gibson (1973)[b]	Birth weight (g)	Lowest Hemoglobin Levels (g per 100 mL)	9	β: -0.002 (-0.003 to -0.001); adj R^2=0.62; p=0.007	Decreased hemoglobin levels with increased birth weight.	M2C
Sagen (1984)	Birth weight and length, both continuous variables	Hemoglobin, stratified into three groups.	877	N/A. Author summary: Birth weight and birth length were significantly different between all three concentrations of hemoglobin ($p<0.0001$)	We did not perform a post-hoc analysis because the data presentation did not permit an effect size calculation or regression analysis.	S5A &B
Scanlon (2000)	Odds of SGA	Hemoglobin levels, stratified into seven groups from very low to very high.	17,303 1	N/A. Author summary: Authors report that the risk of SGA was increased with higher maternal hemoglobin concentrations during the first and second trimesters with little association between 3rd trimester hemoglobin levels and odds of SGA.	We did not perform a post-hoc analysis because the data presentation did not permit an effect size calculation or regression analysis.	S5C

Steer (1995)	Birth weight, continuous variable and odds of LBW (<2500g).	Hemoglobin concentration, stratified into 8 groups.	15,799 6	N/A. Author summary: Hemoglobin levels out-with the normal range lead to increased odds of SGA. In adjusted analyses, odds of LBW was significantly raised below 85 g/l and all concentrations above 105 g/l compared to the reference variable (96-105 g/l; p<0.05). Odds of SGA was only not significant in the group with hemoglobin concentrations between 86-95 g/l.	We did not perform a post-hoc analysis because the data presentation did not permit an effect size calculation or regression analysis.	S5A
von Tempelhoff (2008)	Control (>2500g), n=3959 VS LBW (<2500g), n=473	Hemoglobin (g/dL) at 14-20 wks	4432	MD: 0.25 g/dL decrease in the higher birth weight group (0.16 to 0.34)	Greater hemoglobin levels in the lower birth weight group.	S6B
Whittaker (1996)	Relative birth weight (g)	Hemoglobin (g/dL), 36 weeks	68	β: -0.0008 (-0.0013 to -0.0002); adj R^2=0.09; p=0.008	Decreased hemoglobin with increased birth weight.	M2C
		Hemoglobin mass (g/dL), 36 weeks	51	β: 0.032 (-0.021 to 0.084); adj R^2=0.009; p=0.234	Increased hemoglobin mass with higher birth weight.	M2C

2d. Birth weight vs blood volume (hypothesis: blood volume increases with increasing birth weight).

Reference	Exposure/ Comparator	Outcomes	N	Effect Size (95% CI)	Summary	Fig.
Hytten (1963b)	Birth weight, continuous variable	Blood volume, continuous variable.	109	N/A. Author summary: "blood volume was not related to birth weight after the effect of height had been taken into account". No further data were provided.	No quantitative data were reported.	N/A
Ueland (1976)	Birth weight, stratified into four groups.	Blood volume (L), continuous variable.	75	N/A. Author summary: Non-significant positive trend between blood volume and the categories of increasing birth weight.	We did not perform a post-hoc analysis because birth weight is stratified into more than two groups. Sample sizes per group are not reported.	N/A

3a. PV vs GFR biomarkers (serum levels; hypothesis: serum levels decrease with increasing plasma volume).

Reference	Exposure/ Comparator	Outcomes	N	Effect Size (95% CI)	Summary	Fig.
Gibson (1973)	Plasma volume	Inulin clearance (ml/min)	9	β: 0.036 (-0.0085 to 0.080); adj R^2=0.25; p=0.097	Increasing inulin clearance with increasing plasma volume, although not a significant result.	S5A

3b. Hemoglobin levels vs GFR biomarkers (serum levels; hypothesis: serum levels increase with increasing hemoglobin levels).

Reference	Exposure/ Comparator	Outcomes	N	Effect Size (95% CI)	Summary	Fig.
Gibson (1973)	Lowest Hemoglobin levels	Inulin clearance (ml/min)	9	β: 6.6 (-15.49 to 28.69); adj R^2<0; p=0.503	Increasing inulin clearance with increasing hemoglobin, although not a significant result.	S5A

3c. Extracellular volume vs GFR biomarkers (Uromiro clearance rate; hypothesis: clearance rate increases with increasing extracellular volume).

Reference	Exposure/ Comparator	Outcomes	N	Effect Size (95% CI)	Summary	Fig.
Varga (2000)	Extracellular volume (%	Uromiro clearance (ml/mib),	11	β: -0.81 (-9.29 to 7.67); adj R^2<0; p=0.834	Decreasing Uromiro clrearance with	S5A

	body mass), continuous variable	continuous variable			increased extravaellular volume, although not a significant result.	

Supplementary Material 5: A summary of findings from all of the observational mammalian studies included in the systematic review.

1. Birth weight vs GFR biomarkers (creatinine; hypothesis: creatinine decreases with increasing birth weight).					
Reference	**Exposure/Comparator**	**Outcomes**	**Effect Size (95% CI)**	**Summary**	**Fig.**
Abeni (2004)	Birth weight, stratified into four groups.	Creatinine concentration (log micro mol/L), continuous variable.	N/A. n=59 cows. Creatinine concentration was correlated with birth weight class (R^2=0.815, p=0.004) and was highest in the 41-45kg class (second lightest).	Data were presented as results of an ANOVA. The relationship between birth weight class and creatinine concentration is not linear.	N/A
2. Birth weight vs blood volume (hypothesis: blood volume increases with increasing birth weight).					
Reference	**Exposure/Comparator**	**Outcomes**	**Effect Size (95% CI)**	**Summary**	**Fig.**
Haynes (1954)	Birth weight (g)	Uterine blood volume (cc)	β: 0.146 (0.02 to 0.27); adj R^2=0.66; p=0.031, n=6	Increase in blood volume with increasing birth weight.	S7B

Supplementary Material 6. A summary of findings from all of the experimental mammalian studies included in the systematic review.

1a. Birth weight vs PV (absolute PV; hypothesis: plasma volume increases with increasing birth weight).					
Reference	**Exposure/Comparator**	**Outcomes**	**Effect Size (95% CI)**	**Summary**	**Fig.**
Van Mieghem (2009)	Control (sham operated), n=9 VS Fetoplacental reduction, n=8	Absolute PV (ml)	MDi: 1.9 ml increase in the control group (1.04 to 2.76)	Increase in absolute PV the higher birth weight group	S7A
		Absolute PV/body weight (ml/g)	MDi: 1.6ml/g decrease in the control group (-0.65 to 3.85)	Decrease in PV, adjusted for body weight, in the control group.	S7A
1b. Birth weight vs hematocrit (hypothesis: hematocrit decreases with increasing birth weight).					
Reference	**Exposure/Comparator**	**Outcomes**	**Effect Size (95% CI)**	**Summary**	**Fig.**
Van Mieghem (2009)	Control (sham operated), n=9 VS Fetoplacental reduction, n=8	Hematocrit (%) at gestational day 22	MDi: 3.5% decrease in the control group (1.86 to 5.14)	Decrease in hematocrit in the higher birth weight group.	S7A
1c. Birth weight vs blood volume (hypothesis: blood volume increases with increasing birth weight).					
Reference	**Exposure/Comparator**	**Outcomes**	**Effect Size (95% CI)**	**Summary**	**Fig.**
Rumball (2008)	Birth weight (g)	Blood volume (mL/kg-1)	β: -0.014 (-0.03 to 0.004); adj R^2=0.24; p=0.104, n=9	Decrease in blood volume with increasing birth weight although not a significant relationship.	S7B

Supplementary Material 7. A summary of findings from the observational human and non-human studies included in the systematic review which were not included in any post-hoc analyses and for which figures of the reported data are not presented[1].

Observational Human	**1a. Birth weight vs GFR biomarkers (serum levels or concentration; hypothesis: serum levels or concentration decrease with increasing birth weight).**				
	Reference	**Relationship**	**(n)**	**Author Summary**	**Comments**
			212	"SGA occurred in 30.8% of pregnancies in normotensive women with uric acid in the highest quartile (uric acid >4.1 mg/dL) compared with only 3.4% of normotensive women with uric acid in the lowest quartile (uric acid ≤2.9 mg/dL; P<.001). Uric acid concentrations as a continuous measure were associated with SGA in normotensive women after adjusting for maternal pre-pregnancy BMI and race (odds ratio, 1.06; 95% CI, 1.01–1.12; P <.02). When additionally adjusted for smoking, the magnitude of the association was unaffected, but precision was compromised (odds ratio, 1.05; 95% CI, 0.99 –1.10; P<.09). Uric acid was weakly correlated with smoking (r=0.14; p<.03)."	Data presentation did not permit an effect size calculation or regression analysis.
	1b. Birth weight vs hematocrit (hypothesis: hematocrit decreases with increasing birth weight).				
	Reference	**Relationship**	**(n)**	**Author Summary**	**Comments**
	Blankson (1993)	Odds of IUGR and hematocrit (%), stratified into six groups.	17149	Significantly increased odds of SGA for some comparisons (between 40-42% in black and white women in early pregnancy and hematocrit >40% in white women in late pregnancy).	Sample sizes per group and variance are not reported and the data presentation did not permit an effect size calculation or regression analysis.
	1c. Birth weight vs blood volume levels (hypothesis: blood volume increases with increasing birth weight).				
	Reference	**Relationship**	**(n)**	**Author Summary**	**Comments**
	Hytten (1963b)	Birth weight and blood volume, both continuous variables.	109	"Blood volume was not related to birth weight after the effect of height had been taken into account."	No quantitative data were reported.
	Ueland (1976)	Birth weight, stratified into four groups and blood volume (L), continuous variable.	75	Non-significant positive trend between blood volume and the categories of increasing birth weight.	Birth weight is stratified into more than two groups and sample sizes per group are not reported.
Observational Mammalian	**2. Birth weight vs GFR biomarkers (serum levels; hypothesis: serum levels decrease with increasing birth weight).**				
	Reference	**Relationship**	**(n)**	**Author Summary**	**Comments**
	Abeni (2004)	Birth weight, stratified into four groups and creatinine concentration (log micro mol/L), continuous variable.	59	Creatinine concentration was correlated with birth weight class (R^2=0.815, p=0.004) and was highest in the 41-45kg class (second lightest).	Data were presented as results of an ANOVA. The relationship between birth weight class and creatinine concentration is not linear.

[1] Abbreviations: BMI, body mass index; IUGR, intrauterine growth restriction;SGA, small for gestational age; ANOVA, analysis of variance.

Supplementary Material 8. Quality of evidence ratings for human and non-human evidence streams.

1. Human evidence: initial rating of 'moderate' (N=31 studies; 51,0213 humans)			
Factor		**Rating**	**Rationale**
Downgrade	Risk of bias across studies	0	For eight of the nine risk or bias domains, except conflict of interest, most individual studies were rated 'low' or 'probably low' risk.
	Indirectness	0	The population is directly relevant and the outcomes were considered relevant to human health and the question at hand, respectively.
	Inconsistency	-1	We found consistent evidence of an association between birth weight and PVE (N=25); however there is inconsistent and limited evidence of an association between birth weight and GFR (N=7) and between PVE and GFR (N=2).
	Imprecision	0	The confidence intervals were not judged as being excessively large.
	Publication bias	0	Studies were not considered uniformly small and we conducted a thorough literature search which included meeting abstracts and a reference list search of studies included in the systematic review. We did not find evidence to suggest publication bias.
Upgrade	Large magnitude of effect	0	The magnitude of effect varied between studies.
	Dose response	0	We found evidence of a dose response for hemoglobin levels (surrogate for PVE) and odds of SGA from the two largest studies; however we found evidence of a dose response for the other relationships in the model (Figure 2).
	Confounding minimizes effect	0	There was no evidence to suggest that residual confounding would substantially affect results.
		→	**Overall quality of evidence = 'low'**
2. Non-human observational evidence: initial rating of 'moderate' (N=2 studies; 65 animals)			
Factor		**Rating**	**Rationale**
Downgrade	Risk of bias across studies	0	Both studies were rated 'low' or 'probably low' risk of bias for most of the domains so we considered the studies to be of sufficient quality.
	Indirectness	0	We considered the non-human mammalian evidence to be directly relevant to the human evidence.
	Inconsistency	0	We found only two small relevant studies which assessed different variables and thus were not comparable.
	Imprecision	-1	We found only two relevant studies which were considered too small to provide precise effects estimates. One study on which we were able to calculate a post-hoc effect size had wide confidence intervals.
	Publication bias	0	Both studies were small and we did not contact study authors for potentially missing data. However we conducted a thorough literature search which included meeting abstracts and hand searching the reference list of studies included in the systematic review. Therefore we did not consider there to be any evidence to support a downgrade based on publication bias.
Upgrade	Large magnitude of effect	0	No evidence of a large magnitude of effect.
	Dose response	0	No evidence of a dose response.
	Confounding minimizes effect	0	No evidence that residual confounding would substantially affect results.
		→	**Overall quality of evidence = 'low'**
3. Non-human experimental evidence: initial rating of 'high' (N=2 studies; 26 animals))			
Factor		**Rating**	**Rationale**
Downgrade	Risk of bias across studies	-2	The included studies were at "probably high risk" for a three important risk of bias elements and one study did not report randomization.
	Indirectness	-1	There were only two small studies one of which reported an indirect measure of fetal growth based on external measurements (estimated using growth catheters).
	Inconsistency	0	No pattern of consistent or inconsistent results between the two studies.
	Imprecision	-1	We found only two relevant studies with wide confidence intervals and considered these too small to provide precise effects estimates.
	Publication bias	0	Both studies were small and we did not contact study authors for potentially missing data. However we conducted a thorough literature search which included meeting abstracts and hand searching the reference list of studies included in the systematic review. Therefore we did not consider there to be any evidence to support a downgrade based on publication bias.
		→	**Overall quality of evidence = 'very low'**

Supplementary Material 9. Summary of findings and overall strength of evidence ratings for human and non-human evidence streams[1].

1. Human evidence	
Consideration	**Rationale**
Quality (see Table 6)	'Low.'
Direction of effect	We found evidence of an association between fetal growth and PVE, an inconsistent relationship between fetal growth and GFR, and very limited data on the association between PVE and GFR. For all three relationships in the model, the direction of effect is indeterminate from the existing data.
Confidence in effect	We were confident from two large studies that there is an association between PVE and fetal growth; however we have low confidence in an association between fetal growth and GFR, or PVE and GFR. A single well conducted, adequately powered and designed study could alter our confidence in the strength of the effect of these two relationships.
Other compelling attributes	None.
➔	Overall strength of human evidence = **'inadequate'**
2. Non-human observational evidence	
Consideration	**Rationale**
Quality (See Table 6)	'Low.'
Direction of effect	The direction of effect for all three relationships is indeterminate from the existing data.
Confidence in effect	We have low confidence in the strength and direction of the effect. Thus a well conducted, adequately powered and designed study could alter our confidence in the effect and direction of effect for all three relationships (fetal growth and GFR *or* PVE; and GFR and PVE).
Other compelling attributes	None.
➔	Overall strength of non-human observational evidence = **'inadequate'**
3. Non-human experimental evidence	
Consideration	**Rationale**
Quality (see Table 6)	'Very low.'
Direction of effect	One study suggests that fetal growth precedes change in PVE. The direction of effect between fetal growth and PVE, and PVE and GFR is indeterminate from the existing data.
Confidence in effect	We have low confidence in the strength and direction of the effect. Thus a well conducted, adequately powered and designed study could alter our confidence in the effect and direction of effect for all three relationships (fetal growth and GFR *or* PVE; and GFR and PVE).
Other compelling attributes	None.
➔	Overall strength of non-human experimental evidence = **'inadequate'**

[1] The overall strength of the evidence rating was assigned using the definitions described in Table 3.

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